



# Empagliflozin/Linagliptin (Glyxambi®)

## Abbreviated New Drug Update

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### OVERVIEW<sup>1</sup>

- Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2), and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, combination approved for:
  - ☐ Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.
  - ☐ Not indicated for use in treating type 1 diabetes or diabetic ketoacidosis.
- Contraindications/Warnings/Precautions
  - ☐ Contraindicated in severe renal impairment, end-stage renal disease, or dialysis; history of hypersensitivity to either of these products.
  - ☐ Empagliflozin/linagliptin has not been studied in patients with a history of pancreatitis. Post-marketing reports of acute pancreatitis have been made, including fatal pancreatitis. If suspected, the medication should be discontinued.
  - ☐ Before starting therapy, assess and correct volume status in patients with renal impairment, the elderly, patients with low systolic blood pressure, and patients on diuretics.
  - ☐ Assessment of renal function is recommended prior to starting therapy and periodically thereafter. Empagliflozin/linagliptin should not be started in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m<sup>2</sup>. The medication should be discontinued if the eGFR persistently falls under 45 mL/min/1.73 m<sup>2</sup>. Empagliflozin increases serum creatinine and decreases eGFR, especially in the elderly and inpatients with moderate renal impairment, thus creating an increased need for more frequent monitoring.
  - ☐ Empagliflozin increases the risk of genital mycotic infections and urinary tract infections.
  - ☐ Empagliflozin increases LDL-C.
- Availability
  - ☐ 10 mg empagliflozin/5 mg linagliptin tablet
  - ☐ 25 mg empagliflozin/5 mg linagliptin tablet

- Dosage and Administration
  - ❑ The recommended dose is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, with or without food.
  - ❑ The dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily in the morning, with or without food.
- Adverse events (≥ five percent)
  - ❑ Urinary tract infections
  - ❑ Nasopharyngitis
  - ❑ Upper respiratory tract infections
- Drug interactions
  - ❑ Diuretics (potential volume depletion)
  - ❑ Insulin/insulin secretagogues (increased hypoglycemia)
  - ❑ p-glycoprotein inhibitors or CYP3A4 Enzymes — the efficacy of linagliptin may be reduced when administered with a strong P-gp or CYP3A4 inducer; alternative therapy may be needed.
- Pregnancy Category C
- Clinical Trials
  - ❑ Patients with type 2 diabetes (n=686) were enrolled in a double-blind, active controlled study to compare the empagliflozin 10 mg or 25 mg/linagliptin 5 mg combination to the individual components. After a two-week run-in period, patients who were inadequately controlled on at least 1,500 mg of metformin daily with a HbA1c between seven and 10.5 percent were randomized 1:1:1:1:1 (empagliflozin 10 mg, empagliflozin 25 mg, linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, or empagliflozin 25 mg/linagliptin 5 mg). At week 24, the fixed dose empagliflozin/linagliptin combinations provided statistically significant improvements in HbA1c ( $p<0.0001$ ) and fasting plasma glucose ( $p<0.001$ ) compared to the individual components. The combination treatment also resulted in a statistically significant reduction in body weight compared to linagliptin ( $p<0.0001$ ); however, no statistically significant differences were seen when compared to empagliflozin.

## CLINICAL CONSIDERATIONS<sup>2</sup>

- Several single-entity SGLT2 inhibitors [dapagliflozin (Farxiga™), empagliflozin (Jardiance), and canagliflozin (Invokana™)] and DDP-4 inhibitors [sitagliptin (Januvia®), alogliptin (Nesina®), saxagliptin (Onglyza®) and linagliptin (Tradjenta)] are available in the market place.
- Combination products containing a SGLT2 inhibitor and metformin include canagliflozin and metformin (Invokamet™) and dapagliflozin and metformin (Xigduo® XR). Alogliptin and pioglitazone (Oseni®) is the only DDP4 inhibitor/ thiazolidinediones (TZD) combination product in the market.
- The 2013 American Association of Clinical Endocrinologists (AACE) guidelines suggest SGLT2 inhibitors as a fifth, fourth, and third choice in monotherapy, dual therapy, and triple therapy, respectively.<sup>3</sup> The AACE advises using SGLT2 inhibitors with caution and acknowledges that their place in therapy for diabetes management remains undefined due to lack of experience with these agents.

- The 2015 American Diabetes Association (ADA) Standards of Medical Care in Diabetes have added SGLT2 inhibitors to the management algorithm for type 2 diabetes.<sup>4</sup>
- Glyxambi combines two commercially available products, empagliflozin (Jardiance®; SGLT2 inhibitor) and linagliptin (Tradjenta™; DPP-4 inhibitor), into a fixed combination tablet that can be taken once daily.

## REFERENCES

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1 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2015.

2 Glyxambi [package insert]. Ridgefield, CT; Boehringer Ingelheim; January 2015

3 American Association of Clinical Endocrinologists. AACE Comprehensive Diabetes Management Algorithm Consensus Statement. Endocrine Practice. 2013; 19(2): 1-48. Available at: <https://www.aace.com/publications/algorithm>. Accessed March 4, 2015.

4 American Diabetes Association. Position Statement. Standards in Medical Care in Diabetes - 2015. Diabetes Care. 2015; 37:S14-S80. doi: 10.2337/dc15-S003 Available at: [http://care.diabetesjournals.org/content/38/Supplement\\_1](http://care.diabetesjournals.org/content/38/Supplement_1). Accessed March 19, 2015.